REMARKS

Status Summary

Claims 1-103 are pending. Claims 6, 18, 19, 31, 40-56, 66, 67,70, 71, and 82-103 are withdrawn as directed to non-elected inventions or species. Claims 1-5, 7-17, 20-30, 32-39, 57-65, 68, 69, and 72-81 were examined. Claims 7, 8, 21, 33, 35, 63, and 69 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that does not enable one skilled in the art to practice the invention. Claims 7, 8, 11-13, 21, 33, 35, 63, and 69 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1-5, 7-17, 20-30, 32-39, 57-65, 68, 69, and 72-81 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the documents of record. Claims 1-3, 9-14, 16, and 17 are provisionally rejected under the doctrine of obviousness-type double patenting.

Claims 42-56 and 82-103 are canceled. Claim 20 is withdrawn. Claims 7, 10-13, 21, 24, 26, 33, 35, 63, and 69 are amended. A declaration pursuant to 37 C.F.R. § 1.132 by Dr. Kandasamy Hariharan, a named co-inventor of the instant application, is submitted herewith. Reconsideration in view of the present amendments, remarks, and inventor's declaration is respectfully requested.

Information Disclosure Statement

The examiner states that no information disclosure statement (IDS) has been filed with this application. Official action, page 2, item 4. In a telephone conference with Nancy Berg, assistant to the applicants' representative, on January 5, 2004, the examiner confirmed that the IDS filed April 14, 2003, had been entered. Applicants respectfully request consideration of the documents cited therein, as well as the documents identified in the IDS filed on January 16, 2004. The applicants further request that the properly initialed PTO-1449 forms for both of the aforementioned IDSs be returned to the applicants' representative.

Amendments to the Specification

The examiner objects to the specification for non-capitalization of trade names. The specification is amended to comply with requirements for capitalization of trademarks.

The specification is also amended to clarify the relationship of applications to which the instant application claims priority. A petition pursuant to 37 C.F.R. § 1.78(a) for entry of an unintentionally delayed priority claim is submitted herewith.

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Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 7, 8, 21, 33, 35, 63, and 69 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that does not enable one skilled in the art to practice the invention. In particular, the examiner states that antibodies referred to in the claims, including the IDEC-131, 3E4, 2H5, 2H8, 4D9-8, 4D9-9, 24-31, 24-43, 89-76, RITUXAN®, and B1 antibodies, must be readily available to the public or obtainable by a method set forth in the specification. The examiner also states that the specification should be amended to identify deposit information, if appropriate. Official action, page 3, item 6. This rejection is respectfully traversed.

Cells expressing the RITUXAN® (rituximab) antibody are publicly available as deposit number 69119 from the American Tissue Type Collection (ATCC). A copy of the receipt issued by the ATCC, which confirms deposit of the antibody is submitted herewith. Also enclosed is a copy of a letter from the ATCC, which confirms that the deposited antibody is publicly available. In addition, applicants note that the deposit is not required to practice the invention, given that a skilled artisan could readily prepare the rituximab antibody based on the sequence as disclosed in U.S. Patent No. 5,736,137.

With respect to the 24-31 antibody, which is publicly available as ATCC deposit number HB 11712. The specification is also amended to identify the deposit. Applicants further note that the 24-31 antibody is publicly available from Research Diagnostics Inc. as item # RDI-CD40L-2431. *See* enclosed product information sheet.

With respect to the IDEC-131 antibody, applicants advise that this antibody is a humanized version of the murine monoclonal 24-31 antibody, as stated at page 59, lines 15-16 of the specification. As of the filing date of the present application, a skilled artisan could readily prepare humanized versions of the 24-31 antibody, including IDEC-131, given the sequence of the 24-31 antibody as disclosed in U.S. Patent No. 6,001,358. Methods for preparing humanized versions of 24-31 are also disclosed in the '358 patent.

The 89-76 antibody is available as ATCC deposit number HB 11713. A copy of the deposit receipt is submitted herewith, and the specification is amended accordingly.

The B1 antibody is identified in the claim 6 of U.S. Patent No. 6,565,827, which is directed to a composition comprising "antibody or antibody fragment binds to a binding site on said CD20 antigen that is recognized by a B1 antibody." The specification states that the antibody is available for purchase from Coulter Corporation.

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Based on the foregoing, this rejection of claims is believed to be rendered moot, and withdrawal of the rejection of claims 7, 8, 21, 33, 35, 63, and 69 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 7, 8, 11-13, 21, 33, 35, 63, and 69 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Official action, page 4, item 7. This rejection is also traversed.

Claims 7, 8, 21, 33, 35, 63, and 69, are rejected on the basis that, in the examiner's view, the designations "IDEC-131, 3E4, 2H5, 2H8, 4D9-8, 4D9-9, 24-31, 24-43, 89-76, RITUXAN®, and B1," are indefinite because the characteristics of the antibodies are not known.

Claim 7 is amended to refer to the 24-31 antibody, a humanized 24-31 antibody, and the antibody produced by ATCC deposit number HB 11713. Claims 12, 21, 35, 63, and 69 are amended to refer to the rituximab antibody. Claim 33 is amended to refer to the 24-31 antibody or a humanized 24-31 antibody. Applicants' comments above in response to the rejection of claims under § 112, first paragraph, identify one or more sources by which these antibodies, as well as the B1 antibody, can be obtained or prepared.

With respect to the rituximab antibody, applicants also submit herewith a copy of a letter from the United States Adopted Names Council, which officially recognizes the designation "rituximab,"

With respect to Mab 24-31, applicants reiterate that Mab 24-31 is known in the art and publicly available from Research Diagnostics Inc. under the designation "24-31" as item # RDI-CD40L-2431. A skilled artisan could also readily prepare a humanized antibody based on the disclosure of U.S. Patent No. 6,001,358.

With respect to the 89-76 antibody, claim 7 is amended to refer to the ATCC deposit number.

With respect to the B1 antibody, the specification clearly identifies that B1 antibody as that described in U.S. Patent No. 5,843,398, to which U.S. Patent No. 6,565,827 claims priority. *See* U.S. Application No. 09/855,717 at page 3, lines 19-21.

Claims 7, 8, 21, 33, 35, 63, and 69, are rejected on the basis that the trade names RITUXAN® and IDEC-131 identify the sources from which the antibodies may be obtained

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rather than the antibodies themselves. Initially, applicants note that the use of trade names is acceptable if the product to which the trademark refers has a fixed and definite meaning. *See* MPEP 608.01(v). Applicants submit that the term "RITUXAN®" clearly has a definite meaning as used in the technical and popular literature. Notwithstanding the foregoing, to facilitate prosecution, applicants have amended claim 7 to replace the name "RITUXAN®" with "rituximab." The equivalency of these terms is clearly set forth in the specification. *See* U.S. Application No. 09/855,717 at page 4, line 7. With respect to the designation "IDEC-131," applicants respond that "IDEC-131" is not a trade name. In addition, this designation, has been removed from the claim, and thus the rejection on this basis is rendered moot.

Claims 11-13 are rejected on the basis that the "second antibody" and radiolabel of a radiolabeled second antibody are not identified as required in the examiner's official communication mailed February 11, 2003. Claim 10 is amended to identify the second antibody as an anti-CD20 antibody, and claim 11 is amended to refer to a radiolabeled anti-CD20 antibody. Claim 12 is amended so as to be directed to the anti-CD20 antibodies rituximab, 2B8, and B1. Support for addition of the 2B8 antibody to the claim is found in the originally filed application at page 22, lines 25-28. Claim 13 is amended to refer only to yttrium[90]-labeled anti-CD20 antibodies. In addition, claim 20 is withdrawn. **Upon allowance of a generic claim, the examiner is requested to reconsider rejoinder of claims directed to additional species encompassed by original claims 10-13 and 20.**

Claim 21 is rejected as lacking proper dependency. Claim 21 is amended to depend from claim 20. Claims 24 and 26 are also amended for clarity. No new matter is added.

Based on the foregoing, claims 7, 8, 11-13, 21, 33, 35, 63, and 69 are believed to be sufficiently distinct to meet the requirements of § 112, second paragraph.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-5, 7-17, 20-30, 32-39, 57-65, 68, 69, and 72-81 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,287,537 to Kaminski et al. (Kaminski) and/or U.S. Patent No. 5,843,439 et al. to Anderson et al. (Anderson) in view of Gruss et al. (1997) *Leukemia & Lymphoma* 24:393-422 (Gruss), Carbone et al. (1995) *American Journal of Pathology* 147:912-922 (Carbone), and U.S. Patent No. 6,001,358 to Black et al. (Black). In the view of the examiner, "[g]iven the expression of CD20 and/or CD40, the ordinary artisan would have been motivated to target B cell non-Hodgkin's

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lymphoma directly with radiolabeled CD20-specific antibodies and to diminish activation of said B cell leukemia by blocking activation by CD40 ligand expressing T cells with CD40L-specific antibodies." Official action, pages 5-7, item 9. This rejection is respectfully traversed based on the arguments set forth below.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. In the instant case, the examiner has not met this burden on the following basis: (1) failure to individually consider the claims in view of each of the cited references; and (2) failure to identify a specific suggestion or motivation to perform the presently claimed invention with any reasonable chance of success. In fact, the Gruss journal article cited by the examiner expressly teaches away from the claimed invention.

I. The Rejection is Unclear as to Which Reference(s) Apply to Which Claim(s)

The Manual of Patent Examining Procedure (MPEP) instructs that a plurality of claims should never be grouped together in a common rejection unless equally applicable to all claims in the group. MPEP § 707(d). Notwithstanding this instruction, the examiner has grouped all pending claims into a common obviousness rejection in view of five references. A brief review of the claims and the cited references reveals that all five references are clearly not applicable to each of the claims.

In view of the examiner's grouping of claims together in a common obviousness rejection, it is difficult if not impossible for applicants to address the merits of the rejection on a claim-by-claim basis. MPEP § 706.03 (j) states: "It is important for an examiner to properly communicate the basis for a rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply." Therefore, applicants respectfully request that if the examiner is not persuaded by the additional arguments herein and intends to continue applying some or all of the ten references to the claims in another rejection, then the examiner should do so in the form of another non-final office action to give applicants a fair opportunity to address the merits of the rejection.

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II. The Cited References Do Not Suggest Or Motivate Performance Of The Claimed Invention With A Reasonable Expectation Of Success

The examiner is required to show how and why the applicants would have been motivated to combine the references in the manner combined by the examiner. Although the motivation to combine prior art does not have to be expressly stated in the references themselves, "the examiner must present a convincing line of reasoning" for a proper conclusion that an invention is obvious in view of prior art. *See In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *See also, Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Motivation relies on a reasonable expectation of success.

In contrast to the examiner's assertion, the cited documents do not describe, suggest, or motivate blockade of CD40/CD40L signaling in malignant B cells as an effective therapy. The journal article by Gruss in fact teaches away from the claimed invention, which argues against motivation to perform the claimed invention and, even if the invention were expressly suggested, could not reasonably be expected to be met with success. In support thereof, applicants submit herewith a declaration pursuant to 37 C.F.R. § 1.132 by Dr. Kandasamy Hariharan, a named co-inventor of the present application.

The present invention provides methods for treating B cell lymphoma via blockade of CD40/CD40L signaling in malignant B cells. Claim 1 is reproduced below:

> 1. A method for treating $CD40^+$ malignancies comprising administering a therapeutically effective amount of an antibody or antibody fragment which binds to CD40L thereby inhibiting CD40/CD40L interaction or CD40 signaling.

Initially, applicants note that the Kaminski and Anderson patents are directed to the use of anti-CD20 antibodies for cancer therapy, but do not pertain to anti-CD40L therapies. A skilled artisan would not surmise that successful immunotherapies based on a particular cancer antigen, *e.g.*., CD20, can be generalized as teaching currently undeveloped therapies using any cancer antigen, *e.g.*, anti-CD40L therapies, as now claimed. *See* Hariharan Declaration, statements 10-11. Thus, these documents do not bear on the non-obviousness of the present invention, which is directed to anti-CD40L therapies. Given that Kaminski and Anderson are cited as the primary references, whereas Carbone, Gruss, and Black are cited secondarily, the rejection of claims 1-5, 7-17, 20-30, 32-39, 57-65, 68, 69, and 72-81 under § 103(a) should be withdrawn.

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Although applicants believe that the rejection should be withdrawn based on the foregoing basis alone, the teachings of Gruss, Carbone, and Black are discussed to address clear errors in the examiner's analysis of these documents. When considered alone or in combination, these references also fail to describe, suggest, or motivate blockade of CD40/CD40L signaling in malignant B cells, *e.g.*, by administration of an anti-CD40L antibody antagonist, as an effective therapy. *See* Hariharan Declaration, esp. statements 9, 14, 23.

A skilled artisan would not be motivated to perform the claimed invention with any expectation of success based on the expression of CD40L, as described by Carbone. *See* Hariharan Declaration, statements 15-19. The journal article by Carbone describes detection of CD40 antigen on B lymphoma cells and detection of CD40L on T cells, which distribution is also observed in normal B cells and T cells. Based on the similar expression profile in normal and malignant cells, and the known role for CD40/CD40L signaling in activating B cells, Carbone proposes that CD40/CD40L signaling may also be important for T cell activation of malignant B cells. *See* p. 920, col. 1, ¶ 1. However, Carbone does not demonstrate the function of CD40/CD40L signaling in malignant cells. Carbone expressly acknowledges the interpretational limitations of this study, stating that "[t]he functional significance of the expression of CD40L on reactive T lymphocytes of B-cell NHL also deserves speculation." *See* page 920, col. 1, lines 16-18 (emphasis added). As acknowledged in Carbone, the function of a protein cannot be established by expression alone. Rather, expression data merely invites experimentation to determine protein function in those cells where it is expressed.

A skilled artisan would also not be motivated to perform the claimed invention with any expectation of success based on the studies of Gruss, which actually teach away from the claimed invention. *See* Hariharan Declaration, statements 20-21. The journal article by Gruss describes inhibition of B cell proliferation in the presence of recombinant CD40L. Surprisingly, Gruss suggests a role for CD40/CD40L signaling in malignant cells which is directly opposite to that described in the present application. Gruss states that "[t]he therapeutic use of recombinant human CD40L would be advantageous by providing selective cytotoxicity to tumor cells while stimulating growth of normal B cells." (page 401, col. 1, lines 20-24). Thus, Gruss describes an anti-proliferative or pro-apoptotic effect of CD40/CD40L signaling in malignant cells, which suggests that activation of CD40/CD40L

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signaling may be a viable therapy for B cell malignancies. These results are directly contrary to the present invention.

In contrast to Gruss, the present invention is directed to blockade of CD40/CD40L signaling for treatment of B cell malignancies. The experimental results included in the originally filed application show that CD40/CD40L signaling in malignant B cells has a protective effect, not an anti-proliferative or pro-apoptotic effect as described by Gruss. Indeed, a novel aspect of the present invention is that an anti-CD40L antibody inhibits the cell protective effect of CD40/CD40L signaling in malignant B cells, to thereby enhance the effectiveness of cytotoxic agents, for example, chemotherapeutic agents such as adriamycin. Figure 2A of the application is a bar graph which shows that (1) adriamycin (ADM) induces cytotoxicity of B lymphoma cells (columns 2-3), (2) soluble CD40L (gp39) inhibits ADM-induced cytotoxicity (columns 5-6), and (3) anti-CD40L antibody blocks this survival mechanism (columns 7-8). *See* Hariharan Declaration, statements 12-14, 21.

The Black patent describes anti-CD40L (GP39) antibodies and their use in treating autoimmune disease, which does not pertain to the treatment of B cell malignancies. *See* Hariharan Declaration, statement 22.

Based on the foregoing, it is clear that the cited documents do not teach, suggest, or motivate a treatment method comprising blockade of CD40/CD40L signaling in malignant cells, as now claimed. Given that each of the pending claims are directed, *inter alia*, to blockade of CD40/CD40L signaling, the examiner's additional arguments as to combination therapies do not diminish the novelty and non-obviousness of the invention.

Based on the foregoing arguments, applicants respectfully request that the rejection of claims 1-5, 7-17, 20-30, 32-39, 57-65, 68, 69, and 72-81 under § 103(a) be withdrawn.

Provisional Rejection of Claims
Based on Obviousness-Type Double-Patenting

Claims 1-3, 9-14, 16, and 17 are provisionally rejected under the doctrine of obviousness-type double patenting in view of copending U.S. Application Nos. 09/435,992 and 09/772,938. Official action, page 9, item 11. Applicants may file a terminal disclaimer, if the rejection still stands when one or more claims in the instant application are in condition for allowance.

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Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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